REMARKS

The Examiner rejected claim 13 under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants has amended claim 13 in accordance with the Examiner's suggestion. It respectfully is submitted that the amendment does not introduce new matter and entry and approval of the same is solicited.

Claims 1-13 were rejected under 35 U.S.C. §103(a) as being unpatentable over Loken *et al.*, U.S. Patent No. 5,047,321 ("Loken") in view of Kim *et al*, U.S. Patent No. 5,559,037 ("Kim"), and Inami *et al.*, U.S. Patent No. 5,624,663 ("Inami"). (Paper no. 12, p. 3). Applicants' arguments presented in its response to the Final Office Action of May 17, 2001 were deemed unpersuasive by the Examiner. For the reasons presented below, however, reconsideration and withdrawal of the rejection respectfully is solicited.

Loken discloses a method for multi-parameter analysis of cells in a body fluid sample comprising two nucleic acid dyes and at least one fluorescently labeled cell surface marker (abstract). Loken further discloses analyzing said sample in an automated instrument capable of detecting and recording fluorescence of individual cells (col. 4, lines 37-40).

Kim discloses a method for the simultaneous and quantitative flow cytometric analysis of nucleated red blood cells and white blood cells in a whole blood sample comprising lysing red blood cells from an aliquot of the sample with a diluent to expose the red blood cell cytoplasm to a vital nuclear stain while inhibiting permeation of the stain into the white blood cells (abstract). Kim further discloses passing the diluent/sample mixture through an illuminated optical flow cell causing cells to scatter light and stained nuclei to fluoresce, said scattered and fluorescent light signals are then detected (col. 5, lines 3-10).

Inami discloses a method comprising using a specific dye taken up by erythrocytic nucleated cells so that their nuclei are stained and differentiated by a flow cytometer (abstract). Inami further discloses a two step staining method using a first fluid that is a hypotonic solution comprising a fluorescent dye and a second fluid that is a solution that changes the osmorality and pH of the first fluid (col. 1, lines 56-59).

In making the instant rejection, the Examiner relied on Loken for "teaching" a method comprising "combining a body fluid sample such as whole blood with at least two nucleotide fluorescent dyes such as RNA dye or DNA dye and at least one fluorescent labeled antibody or cell surface marker to form a labeled mixture." and that the labeled mixture "is measured and analyzed using flow cytometric measurements of fluorescence intensity and light scatter for each cell examined." (Paper no. 10, at p. 6).

The Examiner acknowledged, however, that Loken did not disclose "increasing permeability of cytoplasm of specific nucleated cells, specifically erythroblasts using materials such as those in claim 4 of the instant invention, prior to incorporating RNA or DNA dyes thereto." (Paper no. 10, at p. 7). In an Advisory Action issued July 24, 2001 (Paper no. 17) the Examiner further stated that "Loken identified nuclear dyes that can penetrate cell membrane." (Paper no. 17, at page 6) and that "Loken, *et al*, was found to have provided flow cytometric analysis of nucleated cell populations teaching the use of 1) nucleotide dye staining of nuclear material in specific nucleated cell populations and 2) leucocyte cell surface marketer fluorescent labeling..." (Paper no. 17, at page 4).

To fill the acknowledged gap, the Examiner relied on Kim for "teaching" "mixing an aliquot of the blood sample with diluent which rapidly destroys the cytoplasm (lyses) of erythroblasts and erythrocytes and allowing exposure of erythroblastic nuclei while preserving

the integrity and shape of the cytoplasm of leucocytes" which, the Examiner asserted, "have outstanding...qualities." (*Id.*).

To also fill the acknowledged gap, the Examiner relied on Inami for "teaching" "mixing blood with a hypotonic fluorescent dye solution capable of diffusing into erythroblasts to stain their nuclei and a buffer for maintaining pH in the acidic range." (*Id.* paragraph bridging pages 7 and 8).

In the Advisory Action, the Examiner reiterated her position that Kim and Inami do not teach "simultaneous analysis of a sample using 1) erythroblast nucleotide dye staining and 2) leucocyte cell surface marketer fluorescent labeling..." Applicants emphasize that neither Kim nor Inami teach, suggest or disclose use of an antibody label.

Notwithstanding, the Examiner then contended that it would have been obvious to combine the teachings of Kim or Inami with the method of Loken, because, according to the Examiner, "all three cited references utilize flow cytometry in differentiating stained/labeled nucleated cellular populations and Inami specifically suggested using his method in combination with specific nuclear dyes in order to allow better differentiation between erythroblasts and leucocytes," (Paper no. 12, at p. 7) and because, "it allows for simultaneous differentiation between desired populations, in this case, erythroblasts from leucocyte populations." (*Id.*).

These contentions, however, fail to set forth a *prima-facie* case of obviousness. At the very least, the Examiner has not accounted for all elements and limitations of Applicants' claims and the Examiner has identified no disclosure or other factual evidence demonstrating any motivation to combine the cited references. As will be further elaborated below, Applicants respectfully traverse the instant rejection.

I. The References Fail to Account for All Claimed Limitations.

Fundamental to a rejection under §103 obviousness, is that the cited references account for *all* claimed elements and limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974). Merely contending the references may occupy "analogous" fields does not account for the specific limitations and elements of the Applicant's claims. See MPEP §2141.02 (7th Ed., at 2100-94) (Distilling an invention down to the "gist" or "thrust" is improper). Furthermore, it is also fundamental that, to reject claims to a method, the references relied upon by the Examiner must account for the manipulative step claimed. *In re Magat*, 112 USPQ 317, 319 (CCPA 1957). It is simply not sufficient to only account for all material and structural limitations which may also be present in a method claim without accounting for the affirmative active steps claimed that act upon, in or with them.

With these principles in mind, the rejection as set forth by the Examiner stands inapposite to the specific language of the Applicants claims.

Applicants' claim 1, in part, recites:

> *"analyzing the hematologic sample using flow cytometry to detect the nucleotide flourescent signal of the erythroblasts and the flourescent labeled antibody signal of the leucocytes;*
>
> *discriminating between erythroblasts and leucocytes in the hematologic sample and counting the erythroblasts from a difference in nucleotide fluorescent signal of the erythroblast and the flourescent labeled antibody signal of the leucocytes."*

Nothing in Loken indicates that a erythroblast signal is detected by flow cytometry, nor is Loken apparently involved with detecting, discriminating or analyzing erythroblasts. Only in a section referencing light microscopic examination of the already sorted populations is there any mention of erythroblasts, and these are not distinguished from

normoblasts and appear undifferentiated in multiple colored regions. See Loken, Column 10, lines 29-37. Therefore, at the very least, Loken fails to disclose "using flow cytometry to detect the nucleotide fluorescent signal of erythroblasts" and discriminating and counting erythroblasts from a difference in the nucleotide fluorescent signal of the erythroblast. Moreover, the "nucleotide signal of erythroblasts" is not used for discriminating and counting erythroblasts in Loken.

This conclusion is mirrored in the rationale for the rejection wherein the Examiner makes no mention of Loken disclosing flow cytometric analysis of erythroblasts but rather states that Loken discloses "nucleotide dye staining of *nucleic material* in specific nucleated cell populations." (Paper 17, page 4, emphasis added). Applicants, however, do not claim dye staining of "nucleic material" and dye staining "nucleic material" does not per se disclose or render obvious detecting fluorescent nucleotide erythroblast signals.

When it is also considered that, as also recognized by the Examiner, neither Kim nor Inami disclose use of a fluorescent labeled antibody, (Paper 17, pages 3-4), the affirmative manipulative steps taken with respect to the two signal types appearing in Applicants' claims are absent in the cited references. Loken does not disclose fluorescent nucleotide erythroblast signals. Inami and Kim fail to disclose use of a fluorescent labeled antibody signal. While the Examiner contends that these gaps are filled by the references taken in combination, combining the references does not fill the gap as to how these two signals may be acted upon together according to Applicants' method claims. Ad hoc selection of a first type of signal from one reference and second signal type from two other references does not disclose the analysis, detection or discriminating of *both* signals. Therefore, at the very least, the Applicants claimed

steps of *detecting*, *analyzing*, and *discriminating between* these two signals, are necessarily absent and the Examiner's rejection improperly fails to account for them.

In contrast, the standard is clear that "all words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970). Clearly, the words of the manipulative steps embodied in Applicants' method claims have not been properly considered. The rejection therefore fails.

II. The References Lack Evidence Supporting Motivation to Combine.

The Examiner contends that Loken discloses all of the elements of the Applicants' claim save for the step of "raising the permeability of cell membranes," which step, the Examiner alleges, is disclosed by either Kim or Inami. Notwithstanding the lack of disclosure in the cited references accounting for the Applicants claimed manipulative steps, and despite three office actions now addressing the same rejection, the Examiner has yet to identify any portion of Loken which suggests, teaches or motivates its combination with Kim or Inami.

Instead, the Examiner states that motivation is found in 1) the references sharing "the same purpose" as that purpose is defined by the Examiner; 2) that the references "recognize" the importance of accuracy, as such recognition is interpreted by the Examiner; and 3) that the references "teach and suggest improvements in acquiring increased levels of accuracy" to provide a precise diagnosis of disease, as such broad and generalized objective is read by the Examiner in the cited references. None of the above provides any factual motivation or suggestion whatsoever for the combination.

Hindsight motivation and a subjective review is clearly recognized in the Examiner's pronouncement that motivation lies "in differentiating between nucleated hematopoietic cell populations because effective staining technique of nuclear material in different nucleated cell populations, *i.e.*, erythroblastic and leucocyte populations, enables better differentiation therebetween; thereby providing for accurate discrimination, ease, and timely diagnosis of disease in simultaneous nucleated cell differentiation methods." The Examiners opinion as to the contribution implicit in Loken, Inami and Kim to advancement of the field is not relevant. Speculation as to why there may be motivation to combine is not evidence of such motivation. Without evidence of such factual motivation, cited by column and line, from the cited references, no rejection based on §103 may stand.

The MPEP succinctly states, "The mere fact the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP §2143.01 (2000 Ed., 2100-98) Citing, *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990) (emphasis original). In issuing and finalizing the rejection, the Examiner only voices her opinion that the references can be combined, not any suggestion, motivation or disclosure to do so. A *prima facie* case under §103 requires far more than informed speculation.

With all due respect, the Examiner's motivation to combine the references is not relevant. Rather, the question is *where* in the cited references does this motivation to deviate from their teachings appear? *In re Rouffet*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998) (Without a motivation in the references to combine them, the rejection held improper). Should the Examiner maintain the rejection, she is requested to explain "clearly and particularly" *where*

the suggestion and motivation is found in the references of the rejection. *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

Moreover, the Examiner must demonstrate the kind of motivation which would have "*strongly motivated*" ~~one to pick the particular catalyst and temperature limitations required by the claims, and to~~ make a process as claimed *Ex parte Graselli*, 231 USPQ 393, 394 (Bd. App. 1983). The type of motivation required is that which would have "*impelled*" one to do so *Levengood*, 28 USPQ2d at 1302, and the type of suggestion required is that the selection and combination "*should*" be made *Ex parte Markowitz*, 143 USPQ 303, 305 (Bd. App. 1964). The Examiner has not ~~addressed~~ these elements, and without these elements, obviousness cannot be established.

In comparison to these requirements, the Examiner's ~~stated rationale for the~~ rejection is insufficient. Speculation implicit in the Examiner's statements such as that "All three references recognize that effective staining or labeling between the nucleated cell populations is key and requisite to providing accurate differentiation" (Paper no. 17, page 6) not only fails to provide the requisite teaching, or suggestion, it clearly applies an impermissible *per se* rule of obviousness. Such rule is impermissible because the references should not be considered in light of the objectives achieved by the Applicants' invention. *In re Ochiai*, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995) ("reliance on *per se* rules of obviousness is legally incorrect and must cease."); and see MPEP §2116.01 at 2100-45 (Seventh Edition, Rev. 1, Feb. 2000). Generalizations that the combination of references "enables better differentiation" between nucleic materials or "provides for ... timely diagnosis of disease" have no place in this analysis, and are not proper grounds for supporting the rejection.

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Moreover, the Examiner must demonstrate the kind of motivation which would have "*strongly motivated*" one to make a process as claimed, *Ex parte Graselli*, 231 USPQ 393, 394 (Bd. App. 1983). The type of motivation required is that which would have "*impelled*" one to do so, *In re Levengood*, 28 USPQ2d at 1302, and the type of suggestion required is one that demonstrates the selection and combination "*should*" be made, *Ex parte Markowitz*, 143 USPQ 303, 305 (Bd. App. 1964). The Examiner has not demonstrated these elements of motivation, and without these elements, obviousness cannot be established.

In comparison to these requirements, the Examiner's explanation of the motivation supporting the combination underlying the rejection is clearly insufficient. Speculation implicit in the Examiner's statements such as that "All three references recognize that effective staining or labeling between the nucleated cell populations is key and requisite to providing accurate differentiation" (Paper no. 17, page 6) not only fails to provide the requisite motivation, teaching, or suggestion, it clearly applies an impermissible *per se* rule of obviousness. Such rule is impermissible because the references should not be considered in light of the objectives achieved by the Applicants' invention. *In re Ochiai*, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995) ("reliance on *per se* rules of obviousness is legally incorrect and must cease."); and see MPEP §2116.01 at 2100-45 (Seventh Edition, Rev. 1, Feb. 2000). Generalizations that the combination of references "enables better differentiation" between nucleic materials or "provides for ... timely diagnosis of disease" have no place in this analysis, and are not proper grounds for supporting the rejection.

The Examiner's approach thus confuses an intent unspecified in the references with factual disclosure. It is well settled that an obviousness rejection must be based on facts, not generalities. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). "Cold hard facts." *In re Freed*, 165, USPQ 570, 571-72 (CCPA 1970). When a rejection under §103 is not based on facts, it cannot stand. *Ex parte Porter*, 25 USPQ2d 1144, 1147 (BPAI 1992).

In sum, the Examiner has not adduced factual support demonstrating the requisite motivation for the combination of references advanced against Applicants claims. The references, in whatever combination the Examiner may present, fail to account for all the Applicants' claim limitations and lack any disclosure motivating their combination. The Examiner has not met her burden of demonstrating a *prima facie* case of obviousness, therefore, the rejection should be withdrawn.

In view of the foregoing, favorable action on the merits, and allowance of all claims, respectfully is solicited.

Respectfully submitted,

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"Marked-Up" Amendments to Claims Pursuant to Rule 1.121(c)

13. The method according to claim 4 wherein the osmolarity of the mixture [of the leukocytes] is from about 400 mOsm/Kg.H_2O to about 600 mOsm/Kg.H_2O.